

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Jon A. Wolff,
Paul M. Slattum, James E. Hagstrom,
Vladimir G. Budker

Serial No.: 09/631,152

Filed: 08/02/2000

Group Art Unit: 1636

Examiner: Daniel M. Sullivan

For: Gene Expression With Covalently Modified Polynucleotides

Commissioner of Patents
PO Box 1450
Alexandria, VA 2231-1450

APPELLANT'S BRIEF under 37 CFR 1.192

1. Real party in interest:

The real parties in interest are: Jon A. Wolff, Paul M. Slattum, James E. Hagstrom and Vladimir Budker and, by assignment, Mirus Corporation, which has changed its name to MirusBio Corporation under the laws of the State of Delaware and is located at 505 South Rosa Road, Madison, WI 53719.

2. Related appeals and interferences:

There are no interferences known to appellant, the appellant's legal representative, or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

3. Status of Claims:

Claims 1, 3-5 and 7-16 have been rejected and are hereby appealed.
Claims 2, 6 and 17-33 have been canceled.

4. Status of amendments:

No Amendments have been filed subsequent to the final rejection.

5. Summary of Invention:

The present invention is a process for modifying a gene either within or outside an expressible sequence such that the gene can be efficiently expressed in a cell. The expressible gene sequence which is modified can be a part of circular piece of DNA such as a plasmid, or a linear piece of DNA.

The expressible sequence can be modified with any of a wide range of compounds. Compounds can be attached to nucleic acids for a number of different reasons including: marking of the gene sequence for identification within cells, to augment its delivery into the cell over that of unmodified sequences, or to facilitate increased expression of the gene product. A compound can also be attached that would increase the frequency of stable integration of the modified DNA into the genomic DNA of an organism over that which is obtained with unmodified DNA. Efficient stable integration of labeled DNA is highly desirable for creating stable cell transfectants in vitro, transgenic animals, transgenic plants or for gene therapy purposes.

DNA can be efficiently modified covalently on the N7 position of guanine using alkylating agents such as nitrogen mustards, sulfur mustards, epoxides, aziridines, episulfides, dimethylsulfate, molecules containing activated cyclopropyl groups such as the CPI family of molecules, bromoacetamides, or non-covalently using cis-platinum based reagents. Expressible gene sequences modified on the N7 position of guanine can be efficiently expressed following introduction into cells. (Page 14, line 24 to page 15, line 9)

6. Issues:

Whether claims 1, 3-5 and 7-16 are unpatentable under 35 U.S.C. 112, first paragraph because the specification is only enabling for nucleic acid delivery to a cell *in vitro*.

7. Grouping of Claims:

The Board shall select a single claim from the group and shall decide the appeal as to the ground of rejection on the basis of that claim alone.

8. Argument:

(i) Rejection of the Claims under 35 U.S.C. 112, first paragraph.

The initial rejection on page 2 of the Office Action states that claims 1, 3-5 and 7-16 are lacking enablement. On page 3, the Action states that the specification is enabling for a process for nucleic acid delivery to a cell *in vitro*, it does not reasonably provide enablement for a process for nucleic acid delivery to a cell *in vivo*.

Applicants do not understand this reason of rejection for the following reasons: in Example 3 on page 22 of the Specification, DNA covalently modified (alkylated) with digoxin is efficiently expressed in mouse liver hepatocytes following *in vivo* delivery; in Example 4, on page 23, DNA covalently modified (alkylated) with biotin is efficiently expressed in mouse liver hepatocytes following *in vivo* delivery; in Example 5, on page 24, the covalent attachment of a peptide signal (nuclear localizing signal) to an expressible sequence enhances gene expression when delivered to mice, *in vivo*; in Example 6, on page 26, *in vivo* gene delivery of a covalently modified gene sequence results in an enhanced immune response against the plasmid encoded expressible sequence; in Example 8, on page 31, DNA particles formed by the covalent attachment of polycations using a labeling reagent facilitate efficient gene expression *in vivo*.

The examples clearly demonstrate nucleic acid delivery to a cell *in vivo*.

On page 4 the Action indicates that the claims are to be interpreted as claiming therapy. Based on that interpretation, if Applicants are claiming therapy, the claims must be invalid because of the amount of undue experimentation that is required to provide a therapeutic effect.

However, Applicants do not claim therapy. The claims cover delivery of a modified, expressible nucleic acid. Concluding that the claims are intended to cover only therapy is not proper. The Action correctly states that therapeutic references are provided in the Specification. In fact, both the examples and the claims cover delivery and expression of therapeutic proteins. Of course, Applicants are in the process of further developing their methods to provide therapeutic applications to humans. Their efforts to that end are embodied in the claims by providing a patentable tool that can be used for therapeutic purposes.

On page 5 the Action states that therapeutic related experiments are not a patentable utility. The Action cites MPEP §2107.01. Applicants point out that §2701.01 refers to a 35 USC 101 utility rejection instead of the 35 USC 112 rejection upon which the Examiner is relying, nevertheless, the assertion that delivery and expression of a nucleic acid is not a patentable utility is improper.

The Action incorrectly assumes that because Applicants' claims do not refer to a therapy for a genetic disease, there can be no utility for the claim in the field of gene therapy. In contrast to the Office Action's assertion that there is no patentable utility for claiming delivery of a nucleic acid, Applicants are the inventors of granted Patents that claim delivery of various types of nucleic acids. Additionally, there is a multitude of other issued patents that cover delivery of nucleic acids. To state that the Applicants' current set of claims has no patentable utility would contravene the combined reasoning behind all previous issued patents related to nucleic acid delivery only, exclusive of a therapeutic result.



On page 4, the Action states "it is clear from the disclosure that the intended use for the claimed method is gene therapy, and that the method is to be used for gene therapy of extremely complicated diseases such as muscular dystrophy, neurodegenerative disorders, cancer and heart disease." That statement accurately describes an endpoint for which the claimed processes were developed; however, a person having ordinary skill in the art would know that Applicants' methods are a tool to be used as a means to determine compounds that can be used for human therapy as well as a tool to be used when adequate compounds are available to provide therapy to a human. The tool itself is therapeutic if it can be used to develop a therapeutic product.

The Action's reference to MPEP §2107.01 is improperly applied. The MPEP states "Practical utility is a shorthand way of attributing 'real-world' value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public." Applicants have commercialized their nucleic acid delivery inventions by selling them to "the public" in the form of licenses to corporations and universities which are in the industry of

developing methods to provide gene therapy. Therefore, to state that there is no patentable utility is incorrect.

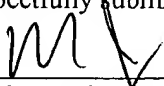
Finally, the Action states that the experiments disclosed in the Declaration were not performed *in vivo*. The examples provided in the Declaration describe transfection of cells in culture. Biologists having ordinary skill in the art consider viable cells in culture to be *in vivo*. Therefore, the experiments disclosed in the Declaration were performed *in vivo* using that common definition. Additionally, as stated earlier in this Brief, Applicants have provided numerous examples in the original specification that show delivery in mammals.

9. Appendix, Copy of the Claims:

1. (previously presented) A process for delivery of a modified expressible nucleic acid to a cell, comprising:
 - a) preparing a nucleic acid molecule having an expressible sequence;
 - b) forming an attachment of a compound, having a molecular weight of 60 kD or less, to the N7 position of a guanine within the expressible sequence of the nucleic acid molecule at a ratio of less than 1 modification per 100 base pairs; and,
 - c) delivering the nucleic acid to a cell wherein expression of the expressible sequence is greater than 50% of the level of expression obtained from the expressible sequence not having a modifying chemical attachment.
2. (canceled) 
3. (original) The process of claim 1 wherein the compound comprises a nucleic acid transfer enhancing signal.
4. (original) The process of claim 3 wherein the nucleic acid transfer enhancing signal is selected from the group consisting of a nuclear localizing signal, a ligand that binds a receptor, and a releasing signal.
5. (previously presented) The process of claim 1 wherein the compound is selected from the group consisting of: an enhanced immune response molecule, an antigen, an antibody, a hapten, a membrane active compound, a peptide, a polymer, a polyion, and a fluorescent compound.
6. (canceled) 
7. (previously presented) The process of claim 1 wherein forming an attachment comprises modifying the nucleic acid using an alkylating molecule.

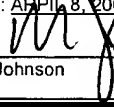
8. (original) The process of claim 7 wherein the alkylating molecule is selected from the group consisting of a mustard and a 3-membered ring system.
9. (original) The process of claim 8 wherein the mustard is selected from the group consisting of a nitrogen mustard and a sulfur mustard.
10. (original) The process of claim 9 wherein the 3-membered ring system is selected from the group consisting of aziridines, oxiranes, cyclopropyls, and episulfides.
11. (original) The process of claim 9 wherein the nitrogen mustard consists of an R-chloride derivative.
12. (previously presented) The process of claim 8 wherein the 3-membered ring system consists of a CPI moiety.
13. (original) The process of claim 1 wherein the nucleic acid consists of double-stranded and single stranded DNA.
14. (currently amended) The process of claim 1 wherein forming an attachment comprises forming a Lewis acid:Lewis base complex between the compound and the nucleic acid, wherein the Lewis acid is not hydrogen.
15. (previously presented) The process of claim 14 wherein the Lewis acid is a transition metal.
16. (previously presented) The process of claim 15 wherein the Lewis acid is platinum.
17. (canceled)
- 18-33. (canceled)

These pages 1-8 are
respectfully submitted,



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Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on
this date: April 8, 2005.



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